below. In particular, to more accurately describe the claimed invention, claims 1 and 31 have been amended to recite that "the non-toxic, proteolytic fragment of tetanus toxin comprises a fragment C and at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C." Support for this amendment can be found throughout the specification, including, for example, at page 19 and in original claim 6. Claims 1 and 31 were further amended by deleting the superfluous term "spinal cord." This amendment was not intended to alter the scope of claims 1 and 31, since, by definition, the spinal cord is part of the central nervous system (CNS). Therefore, in claim 1, administering the fusion protein into the CNS includes administering the fusion protein into the spinal cord. Similarly, in claim 31, the term "a CNS disease" encompasses diseases of the spinal cord.

Claims 32-37 have been added. Support for claims 32-35 can be found in original claim 8 and at page 18 of the specification. Support for claims 36 and 37 can be found in the specification, including, for example, page 19 and Figure 1.

Accordingly, this amendment does not introduce any new matter.

Priority

The Office asserts that this application does not comply with the conditions for receiving the benefit of a prior application under 35 U.S.C. § 119(e) because the first sentence of the specification does not refer to the prior application. (Paper No. 9, p. 3, ¶ 3.) Applicants filed this application as a continuation application of PCT/EP98/05113, filed August 12, 1998. At the time of filing, applicants also claimed the right to priority based on U.S. Provisional Application Nos. 60/055,615 and 60/065,236, filed August 14,

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1997, and November 13, 1997, respectively. Applicants have now amended the specification to include a reference to these related applications. Accordingly, applicants respectfully submit they have complied with the necessary conditions for receiving the benefit under 35 U.S.C. § 119(e) of the earlier filing date of U.S. Provisional Application Nos. 60/055,615 and 60/065,236.

Information Disclosure Statement

The Office asserts that the information disclosure statement ("IDS") filed May 9, 2000, fails to comply with 37 C.F.R. §§ 1.97 and 1.98 and M.P.E.P. § 609, because no translation has been provided for EP 0030496. (Paper No. 9, p. 4, ¶ 4.) As explained in the May 9, 2000, IDS, EP 0030496 is related to the same family as two Canadian applications, CA 1152493 and CA 1178949, both of which were submitted in the May 9, 2000, IDS, along with EP 0030496. Therefore, these English language documents can serve as the English translation of EP 0030496.

Abstract

The Office indicates that this application does not contain an abstract of the disclosure as required by 37 C.F.R. § 1.72(b). (Paper No. 9, p. 4, ¶ 5.) Applicants submit herewith an abstract of the disclosure on a separate sheet that complies with 37 C.F.R. § 1.72(b).

Rejection Under 35 U.S.C. § 112, First Paragraph

The Office rejects claims 1-11 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a

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way to make and/or use the invention. (Paper No. 9, p. 7, ¶ 8.) Specifically, the Office notes that the claims recite "said composition is capable of in vivo retrograde axonal transport," and asserts that neither the specification nor the prior art indicates that "the *entire* composition . . . i.e., the protein *and any carrier/buffer or any other component of the composition* [could] be transported." (*Id.;* emphasis added.) Applicants respectfully traverse this rejection.

Although applicants respectfully disagree, claim 1 has been amended rendering this rejection moot. The amendment was not made in response to this 35 U.S.C. § 112, first paragraph, rejection. Rather, applicants amended claim 1 to more accurately describe their claimed invention. As amended, claim 1 is directed to a method for *in vivo* delivery of a fusion protein. Amended claim 1 further recites that the fusion protein undergoes *in vivo* retrograde axonal transport and transynaptic transport. And, commensurate with the scope of claim 1, the specification enables one of skill in the art to make and use fusion proteins capable of *in vivo* retrograde axonal transport and transynaptic transport. Accordingly, applicants respectfully request withdrawal of this 35 U.S.C. § 112, first paragraph, rejection.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Office rejects claims 1-11 and 31 under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention for the six reasons found on pages 4-7 of the outstanding Office Action. (Paper No. 9, pp. 4-7, ¶ 6.) Applicants address each of the rejections, as enumerated below.

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(1) The term "in association with"

The Office rejects the pending claims, urging that the meaning of the term "in association with," appearing in claim 1, is unclear. (Paper No. 9, p. 5.) The Office acknowledges that the specification defines this term as "an association obtained by genetic recombination," but asserts that this definition does not determine the subject matter encompassed by the claim. (*Id.*) Specifically, the Office asserts that it is unclear whether "in association with" refers to fusion proteins as disclosed by Francis et al., or whether it also encompasses covalent conjugation of a protein to the proteolytic tetanus toxin fragment, as disclosed by Fishman et al. (*Id.*) Although applicants respectfully disagree, the term "in association with" no longer appears in the pending claims, rendering this rejection moot.

(2) The term "molecule having a biological function"

The Office rejects the pending claims, asserting that neither the specification nor the claims define "biological function" so as to apprise the skilled artisan of the subject matter encompassed by the claims. (*Id.* at 5-6.) Applicants respectfully disagree since claim 1 recites that the "molecule with a biological function *comprises a protein*." Applicants submit that the term "protein" is definite. Nevertheless, to expedite prosecution, applicants have deleted the term "a molecule having a biological function" from claim 1. Thus, this ground for rejection should be withdrawn.

(3) The term "a protein for compensation or modulation of functions under the control of the CNS or the spinal cord or modulation of functions in the CNS or the spinal cord"

The Office rejects claims 6 and 7 for reciting the term "a protein for compensation or modulation of functions under the control of the CNS or the spinal cord or modulation

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of functions in the CNS or the spinal cord." (*Id.* at 6.) The Office asserts that the specification does not define the term. Although applicants respectfully disagree, in an effort to expedite prosecution, claims 6 and 7 have been canceled, rendering this rejection moot.

(4) The terms "like and "such as"

The Office rejects claim 8 and those claims depending therefrom, because it is allegedly unclear whether the recitations following the terms "like" and "such as" are part of the claimed invention. (*Id.*) Applicants have amended claim 8 by removing these terms. The recitations in claim 8 following the term "like" and "such as" have also been deleted and now appear in new claims 32 and 33, which depend from claim 8. These amendments do not narrow the scope of claim 8. Applicants respectfully request withdrawal of this rejection.

(5) The term "protein SM"

The Office rejects claim 8 for reciting a "protein SM" asserting there is no art-recognized definition of this term. (*Id.*) The Office notes that "protein SM" may represent a minor typographical error, as page 10 of the specification refers to a "protein SMN." Applicants have amended claim 8 by replacing "protein SM" with "protein SMN," thereby correcting this typographical error. This amendment does not narrow the scope of claim 8, since "protein SM" was clearly intended to refer to "protein SMN." Thus, this ground for rejection should be withdrawn.

(6) The term "therapeutically effective manner"

The Office rejects claim 31, asserting that "the claim does not specify what in particular the therapy is effective for, therefore the metes and bounds of the claim

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cannot be determined." (*Id.* at 7.) Applicants respectfully disagree. "Acceptability of claim language depends on whether one of ordinary skill in the art would understand what is claimed in light of the specification." M.P.E.P. § 2173.05(b). Page 5 of the specification states that applicants' compositions are useful for treating a patient affected by CNS disease. The specification further explains that the therapeutic methods of this invention are "particularly useful for treating neurodegenerative and motoneuron diseases, such as amytrophy lateral sclerosis (ALS, 35), spinal muscular atrophies (SMA, 36, 37), or neurodegenerative lysosomal storage diseases (38, 39)." (Specification, p. 18.) Claim 31 is directed to a method of treating a CNS disease. Thus, in view of the specification, one of ordinary skill in the art would have been reasonably apprised that the composition of claim 31 is effective for treating a CNS disease, including neurodegenerative and motoneuron diseases. Nevertheless, in an effort to expedite prosecution, applicants have deleted the term "therapeutically effective manner" from claim 31, obviating this rejection. This amendment does not narrow the scope of claim 31, since the term "therapeutically effective manner," as used in claim 31, is superfluous.

Rejections Under 35 U.S.C. § 102

(1) Boucher et al.

The Office rejects claim 1 as allegedly anticipated under 35 U.S.C. § 102(b) by Boucher et al. (Paper No. 9, p. 8, ¶ 10.) The Office asserts that Boucher et al. teach an *in vivo* method for delivery of a composition comprising a nonproteolytic fragment of tetanus toxin C fragment recombinantly fused to a second protein (pertussis toxin). (*Id.*) The Office further asserts that such a composition would be expected to be capable of

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in vivo retrograde transport and transynaptic transport into the CNS, absent evidence to the contrary. (*Id.*) Applicants respectfully traverse this rejection.

Boucher et al. teach the immunization of mice and guinea pigs with a recombinant fusion protein ("p75") obtained by combining a pertussis toxin S1 subunit with fragment C of tetanus toxin. Mice were immunized intraperitoneally or subcutaneously with p75. Boucher et al. do not teach applicants' claimed invention.

First, the p75 fusion protein of Boucher et al. includes fragment C of tetanus toxin. On the other hand, the fusion protein recited in the pending claims includes fragment C and at least the 11 amino acids of fragment B that immediately precede the amino terminus of fragment C. Boucher et al. do not teach a tetanus toxin fragment having at least the 11 amino acids of fragment B that immediately precede the amino terminus of fragment C. Accordingly, for these reason alone, Boucher et al. do not teach every element of the claimed invention.

Furthermore, Boucher et al. do not disclose *in vivo* transynaptic transport of the fusion protein in the CNS as recited in the pending claims. The Office asserts, without any supporting evidence, that the p75 fusion protein "would be expected to be capable of *in vivo* . . . transynaptic transport." (Paper No. 9, p. 8.) In essence, the Office asserts that the p75 fusion protein of Boucher et al. is inherently capable of *in vivo* transynaptic transport.

As indicated in the M.P.E.P.

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities

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> or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'

M.P.E.P. § 2112 (quoting *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949, 1950-51 (Fed. Cir. 1999)).

Moreover, "[I]n relying on a theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." M.P.E.P. § 2112 (quoting *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat App. & Int. 1990)). In the instant rejection, the Office has provided no objective evidence or cogent technical reasoning to support a conclusion of inherency. Furthermore, the extrinsic evidence indicates just the opposite. Before applicants' work, no one had ever demonstrated the *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. Accordingly, for this additional reason, applicants respectfully request withdrawal of this rejection.

(2) U.S. Patent No. 5,780,024

The Office rejects claims 1-5 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,780,024 ("the '024 patent"). (Paper No. 9, pp. 8-9, ¶ 11.) The Office asserts that the '024 patent teaches an *in vivo* method for delivery of a composition comprising the tetanus toxin C fragment recombinantly fused to a second protein (SOD-1). (*Id.* at 9.) The Office further asserts that the '024 patent demonstrates that "the fusion protein is capable of in vivo retrograde axonal transport and transynaptic transport in to [sic, into] the CNS (e.g., from systemic administration to the brain stem, see col 1)." (*Id.*) Applicants respectfully traverse this rejection.

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Claim 1 recites that the tetanus toxin portion of the fusion protein comprises a fragment C and at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C. The '024 patent does not disclose a tetanus toxin fragment that includes at least the 11 amino acid residues of fragment B immediately preceding the amino terminus of fragment C.[1] For this reason alone, the '024 patent does not teach each and every element of the claimed invention.

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1 In a subsequent 35 U.S.C. § 103 rejection, the Office acknowledges that the '024 patent does not disclose adding at least 11 amino acids of the tetanus toxin fragment B to the tetanus toxin fragment C. (Paper No. 9, pp. 9-10, ¶ 13.) The Office asserts, however, that Fairweather et al. disclose a recombinant tetanus toxin fragment C including at least 11 amino acids of fragment B (i.e., pTet18). (*Id.*) The Office further asserts that the motivation to combine the references is provided by the references themselves. (Id.) Applicants respectfully assert that there is no motivation in the references themselves to combine the reference teachings.

Fairweather et al. immunized mice with various tetanus toxin constructs, including fragment C (451 amino acids), a 441 amino acid portion of fragment C fused to part of the *E. coli* trpE protein (pTet11), and fragment C plus the last 121 amino acids of fragment B (pTet 18). Fairweather et al. investigated whether these tetanus toxin constructs induced the formation of neutralizing antibodies in mice; the reference mentions nothing about the effectiveness of these tetanus toxin constructs in mediating *in vivo* retrograde axonal transport or transynaptic transport. The Office alleges that the motivation to combine references can be found in Fairweather et al., which allegedly teach that the pTet18 tetanus toxin was easier to obtain than a protein containing only fragment C of the tetanus toxin (i.e., pTet11). (Paper No. 9, p. 10.) There is no indication in the '024 patent, however, that the fusion proteins disclosed therein were difficult to obtain. Indeed, obtaining the desired fusion protein appears straightforward. Col. 5, lines 27-55. Furthermore, the pTet11 construct of Fairweather et al. is not a "protein containing only the C fragment" of the tetanus toxin, as asserted by the Office. (Paper No. 9, p. 10.) The pTet11 construct is missing 10 amino acid residues of fragment C, and there is no evidence that such a construct retains the properties of the full-length fragment C protein. Thus, one can not draw conclusions about the properties of pTet18 relative to the fragment C-containing hybrid proteins of the '024 patent, based on comparisons in Fairweather et al. between pTet18 and pTet11, which does not even contain a full-length fragment C.

The Office further asserts that the motivation to combine the references may be found in the '024 patent based on the alleged teaching that additional amino acids may be added to fragment C as a matter of routine optimization. (Paper No. 9, p. 9.) The '024 patent states that "[a]dditional amino acid residues may be present at the ends of

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Furthermore, the '024 patent does not disclose *in vivo* transynaptic transport of a fusion protein. The Office asserts that the SOD-1/TTC fusion protein of the '024 patent is capable of *in vivo* transynaptic transport, relying on the following statement at column 1 of the '024 patent: "Tetanus toxin, when administered systemically or intramuscularly to animals, is selectively taken up by motor neurons in the brainstem and spinal cord (Habermann et al. (1973) *Naunyn-Schmiedebergs Arch. Pharmacol.* 276: 327-340)" This statement refers to the intact 150 kDa tetanus toxin, not the SOD-1/TTC fusion protein disclosed in the '024 patent. Moreover, the selective uptake of the tetanus toxin by motor neurons in the brainstem and spinal cord refers to *in vivo* retrograde transport—not *in vivo* transynaptic transport. As explained in the specification:

> The axonal retrograde transport begins at the muscle level, where the composition of interest is taken up at the neuromuscular junction, and migrates to the neuronal body of the motoneurons (which are also called the first order neurons) in the CNS or spinal cord. First order neurons mean neurons that have internalized the composition of interest, and thus in this case, correspond to motoneurons.

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the hybrid protein moieties without disrupting hybrid protein function. Such optional additional amino acid residues may be artifacts of the plasmid construction process, and may be left in place as a matter of convenience." Col. 6, lines 38-42. Thus, the '024 patent does not teach adding amino acids to fragment C as a matter of routine optimization. Rather the '024 patent indicates that, as a matter of convenience, additional amino acids can be present at the ends of the hybrid protein moieties, provided they do not disrupt the function of the hybrid protein. This statement in the '024 patent provides no motivation to combine the teachings of the '024 patent with Fairweather et al., particularly since Fairweather et al. is silent with respect to the function of the pTet18 construct, i.e., whether the pTet18 construct "retains the neuronal binding and uptake properties of the holotoxin without the toxic domains." Col. 1, lines 64-67. Thus, any alleged motivation to combine these references based on the '024 patent is inappropriate hindsight reconstruction based solely on the teachings of the present specification. *See In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988.)

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> The transynaptic retrograde transport corresponds to interneuron communications via the synapses from the motoneurons, and comprises second order neurons and higher order neurons (fourth order corresponding to neurons in the cerebral cortex).

Specification, page 12.

Thus, the specification distinguishes between transport across the synapse that connects two neurons (i.e., transynaptic transport) and the uptake of compositions by a motoneuron at the neuromuscular junction followed by migration through the motoneuron (i.e., axonal retrograde transport). The '024 patent does not disclose transynaptic transport of the SOD-1/TTC fusion protein. As explained in the '024 patent: "The present invention provides a SOD-1/TTC hybrid protein and DNA encoding the hybrid protein. The SOD-2/TTC hybrid protein combines the following properties: (1) it exhibits Cu/Zn SOD enzymatic activity; (2) it selectively binds to, and is taken up by, nerve cells, i.e., neurons; and (3) it retains substantial SOD enzymatic activity following cellular uptake." Col. 3, line 65 through Col. 4, line 5. There is no mention of *in vivo* transynaptic transport.

The '024 patent insinuates that the SOD-1/TTC fusion protein may be transported from the peripheral nervous system in to the CNS "[b]y virtue of TTC-mediated uptake by neurons, retrograde axonal transport within neurons, *and* retrograde transsynaptic transfer between neurons[.]" Col. 4, lines 37-43 (emphasis added). But the '024 patent does not demonstrate any such transynaptic transport. Column 16 of the '024 patent describes an experiment allegedly showing the uptake and retrograde axonal transport of a SOD-1/TTC fusion protein in motor neurons. Following intramuscular injection of the SOD-1/TTC fusion protein into the tongue, the

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fusion protein was observed in the cell bodies of the tongue motor neurons. Col. 16, lines 14-36. This experiment thus demonstrates uptake of the fusion protein into tongue motor neurons through the neuromuscular junction, i.e., axonal retrograde transport. But the experiment does not demonstrate transport of the fusion protein between two neurons. Thus, it does not show transynaptic transport of the fusion protein.

Rather, applicants were the first to demonstrate *in vivo* transynaptic transport using a fusion protein containing a tetanus toxin fragment. For example, as explained in the specification, following administration of applicants' β-gal-TTC fusion protein, β-galactosidase activity was detected in the hypoglossal nucleus, i.e., the tongue motor neurons (Example 7) *and* also in connected neurons of the brainstem areas (Example 8). Specification, pages 26-31. Accordingly, for the reasons discussed above, applicants respectfully request withdrawal of this 35 U.S.C. § 102 rejection.

Rejections Under 35 U.S.C. § 103

(1) Rejections based on the '024 patent

The Office made the following rejections under 35 U.S.C. § 103 based on the '024 patent:

1. Claims 6-8, 11, and 31 were rejected as allegedly obvious in view of the '024 patent, as applied to claims 1-5, and further in view of Fairweather et al. (Paper No. 9, p. 9, ¶ 13.)

2. Claims 9 and 10 were rejected as allegedly obvious over the '024 patent in view of Fairweather et al., as applied to claims 6-8, 11, and 31, and further in view of Fishman. (Paper No. 9, pp. 10-11, ¶ 14.)

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3. Claims 6-8, 11, and 31 were rejected as allegedly obvious over the '024 patent in view of Fairweather et al., as applied to claims 6-8, and further in view of U.S. Patent No. 6,159,948. (Paper No. 9, pp. 11-12, ¶ 15.)

Applicants respectfully traverse each of these rejections.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the reference (or references when combined) must teach or suggest all elements of the claim. *See* M.P.E.P. § 2143.

As discussed above, the '024 patent does not disclose *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. The remaining references relied on by the Office, Fairweather et al., Fishman et al., and U.S. Patent No. 6,159,948, fail to remedy the deficiencies of the '024 patent. None of these secondary references teaches or suggests the *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. Accordingly, applicants respectfully request withdrawal of these 35 U.S.C. § 103 rejections.

(2) Rejections based on Francis et al.

The Office asserts that Francis et al. teach an *in vitro* method for delivery of a composition comprising the tetanus toxin C fragment recombinantly fused to a second protein (SOD-1)[2]. (Paper No. 9, p. 12, ¶ 16.) The Office acknowledges that Francis et

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2 Applicants note that the authors of Francis et al. are the same as the named inventors of the '024 patent and that the SOD:Tet451 fusion protein disclosed in Francis

al. do not disclose an *in vivo* method for delivering the fusion protein, however, the Office asserts that Francis et al. propose such an *in vivo* delivery method. (*Id.*) For example, the Abstract states that "SOD:Tet451 may prove to be a useful agent for the targeted delivery of SOD-1 to neurons." Therefore, the Office asserts that it would have been obvious to one of ordinary skill in the art to use the *in vitro* method of Francis et al. in an *in vivo* method, as required by the claims, with a reasonable expectation of success. (*Id.*) Applicants respectfully traverse this rejection.

Claim 1 recites that the tetanus toxin portion of the fusion protein comprises a fragment C and at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C. Francis et al. do not disclose a tetanus toxin fragment that includes at least the 11 amino acid residues of fragment B immediately preceding the amino terminus of fragment C.[3] For this reason alone, Francis et al. do not teach each and every element of the claimed invention.[4]

Furthermore, Francis et al. do not disclose *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. The Office asserts that absent evidence to the contrary, the fusion protein is capable of *in vivo* retrograde axonal transport and transynaptic transport in the CNS. (Paper No. 9, p. 16.) The Office asserts that the SOD-1/TTC fusion protein of the '024 patent is capable of *in vivo*

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et al. appears to be the same as the SOD:Tet451 fusion protein disclosed in the '024 patent.

3 Indeed, the Office acknowledges that Francis et al do not teach adding at least 11 amino acids of the tetanus toxin fragment B to the tetanus toxin fragment C. (Paper No. 9, p. 13, ¶ 17.)

4 Fairweather et al., discussed previously, cannot remedy the deficiencies of Francis et al. For the same reasons that there is no motivation to combine the teachings of the '024 patent and Fairweather et al., there is similarly no motivation to combine the teachings of Fairweather et al. with those of Francis et al.

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retrograde axonal transport and transynaptic transport, relying on the following statement at page 15434 of Francis et al.: "Tetanus toxin has a well-documented capacity for neuronal binding and internalization (19-21). In particular, when administered systemically or intramuscularly to animals, the toxin is selectively taken up by motor neurons in the brainstem and spinal cord (22)." As discussed above regarding the '024 patent, the statement refers to the intact 150 kDa tetanus toxin, not the SOD:Tet451 fusion protein disclosed in Francis et al. Moreover, the selective uptake of the tetanus toxin by motor neurons in the brainstem and spinal cord refers to *in vivo* retrograde axonal transport—not *in vivo* transynaptic transport.

Francis et al. also state that "[t]he carboxyl 451-amino acid fragment of the heavy chain (tetanus toxin fragment C or TTC) retains the neuronal binding and uptake properties of the holotoxin without the toxic domains (23-25)." Francis et al., p. 15434. But again this refers to retrograde axonal transport and not transynaptic transport. Francis et al. do not disclose transynaptic transport of the SOD:Tet451 fusion protein. Rather, applicants were the first to demonstrate *in vivo* transynaptic transport using a fusion protein containing a tetanus toxin fragment. Accordingly, applicants respectfully request withdrawal of this 35 U.S.C. § 103 rejection in view of Francis et al.

The Office made the following rejections under 35 U.S.C. § 103 based on Francis et al.:

1 Claims 6-8, 11, and 31 were rejected as allegedly obvious in view of the Francis et al., as applied to claims 1-5, and further in view of Fairweather et al. (Paper No. 9, pp. 13-14, ¶ 17.)

2. Claims 9 and 10 were rejected as allegedly obvious over Francis et al. in

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view of Fairweather et al., as applied to claims 6-8, 11, and 31, and further in view of Fishman. (Paper No. 9, pp. 14-15, ¶ 18.)

3. Claims 6-8, 11, and 31 were rejected as allegedly obvious over Francis et al. in view of Fairweather et al., as applied to claims 6-8, and further in view of U.S. Patent No. 6,159,948. (Paper No. 9, pp. 15-16, ¶ 19.)

4. Claims 6-8, 11, and 31 were rejected as allegedly obvious over Francis et al. in view of Fairweather et al., as applied to claims 6-8, and further in view of Liston et al. (Paper No. 9, pp. 16-17, ¶ 20.)

Applicants respectfully traverse each of these rejections.

As discussed above, Francis et al. do not teach every element of applicants' claimed invention. Specifically, Francis et al. do not teach *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. The remaining references relied on by the Office, Fairweather et al., Fishman et al., U.S. Patent No. 6,159,948, and Liston et al. fail to remedy the deficiencies of the '024 patent. None of these secondary references teaches or suggests the *in vivo* transynaptic transport of a fusion protein containing a tetanus toxin fragment. Accordingly, applicants respectfully request withdrawal of these 35 U.S.C. § 103 rejections.

CONCLUSION

In view of the foregoing remarks, applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims.

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Respectfully submitted,

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Dated: April 4, 2002

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